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Joint space narrowing and Kellgren–Lawrence progression in knee osteoarthritis: an analytic literature synthesis[1]

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Summary

Objective: While the interpretation of cartilage findings on magnetic resonance imaging (MRI) evolves, plain radiography remains the standard method for assessing progression of knee osteoarthritis (OA). We sought to describe factors that explain variability in published estimates of radiographic progression in knee OA.

Design: We searched PubMed between January 1985 and October 2006 to identify studies that assessed radiographic progression using either joint space narrowing (JSN) or the Kellgren–Lawrence (K–L) scale. We extracted cohort characteristics [age, gender, and body mass index (BMI)] and technical and other study factors (radiographic approach, study design, OA-related cohort composition). We performed meta-regression analyses of the effects of these variables on both JSN and K–L progression.

Results: Of 239 manuscripts identified, 34 met inclusion criteria. The mean estimated annual JSN rate was 0.13 ± 0.15 mm/year. While we found no significant association between JSN and radiographic approach among observational studies, full extension was associated with greater estimated JSN among randomized control trials (RCTs). Overall, observational studies that used the semi-flexed approach reported greater JSN than RCTs that used the same approach. The overall mean risk of K–L progression by at least one grade was $5.6 \pm 4.9\%$, with higher risk associated with shorter study duration, OA definition (K–L ≥ 2 vs K–L ≥ 1) and cohorts composed of subjects with both incident and prevalent OA.

Conclusion: While radiographic approach and study design were associated with JSN, OA definition, cohort composition and study duration were associated with risk of K–L progression. These findings may inform the design of disease modifying osteoarthritis drug (DMOAD) trials and assist clinicians in optimal timing of OA treatments.

Key words: Osteoarthritis, Knee, Radiology, Literature review.

Introduction

Osteoarthritis (OA) affects more than 21 million people in the USA[1], with 36% of elderly Americans aged 70 or older having some degree of radiographic knee OA[2,3]. The prevalence of OA continues to grow as the population ages. Currently available medications for knee OA ameliorate pain without slowing structural progression associated with the disease. Disease modifying osteoarthritis drugs (DMOADs) are still in early stages of development and testing[4]. In this era of active work on DMOAD development, it is critical to determine the expected 'natural history' rate of structural knee OA progression, as this is a key parameter that could be affected by disease modifying therapy.

Magnetic resonance imaging (MRI) may eventually eclipse plain radiography as the modality of choice for documenting structural progression in OA. However, the interpretation of cartilage findings on MRI is still evolving and plain radiography remains the standard method for assessing progression. The measurement of radiographic joint space width is the most accepted and widely used method of assessing OA progression. As it has been shown to be sensitive to change[5], joint space narrowing (JSN) has remained the primary outcome by which DMOAD trials have tested drug efficacy so far[6,7]. Yet, the rate of JSN among cohorts with knee OA exhibits variability[8–10], potentially stemming from differences caused by changing patient characteristics and clinical status over time, inconsistent radiographic positioning of the knee during serial X-ray visits, and other technical factors[8]. With the

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promise of effective DMOAD therapy on the horizon, it is crucial to establish factors affecting the rate of JSN across various study settings.

Another common metric of OA progression is the Kellgren–Lawrence (K–L) scale, traditionally used to assess the severity of radiographic knee OA. This categorical scale incorporates important radiographic features of OA (JSN and osteophyte development) into one scale of increasing severity[11]. The use of the K–L scale has been criticized because its individual categories are not equidistant from each other[12]. Consequently, estimates of the proportion of patients that progress from one category to the next may not be comparable for all starting points. Since the K–L scale is still used in clinical settings for making treatment decisions, its value in assessing knee OA progression warrants continued investigation.

The goal of this analytic review is to describe the variability in estimates of knee OA progression (JSN and K–L) from the published literature and to identify factors explaining this variability. The potential predictors we examined included study and technical factors (study design, year of study publication, study duration, sample size, reader reliability assessment, radiographic definition of OA, radiographic approach used), and cohort characteristics [age, gender, body mass index (BMI), baseline joint space width, and OA-related cohort composition].

Methods

SEARCH STRATEGY

We conducted a search of the PubMed database for relevant studies published between January 1985 and October 2006. We used the key words *OA* and *knee*, in combination with one or more of the following: *progression (or change), radiograph (or X-ray), JSN* and *K–L*. The first author screened through abstracts identified by the search. For abstracts that assessed JSN, we included for further review those studies in which the patient sample had evidence of knee OA, progression was assessed radiographically over time, and sample size was greater than 10. For abstracts that assessed JSN, we included studies in which the patient sample had evidence of knee OA, progression was assessed radiographically over time, and sample size was greater than 10. Abstracts that analyzed K–L progression and examined OA incidence were also eligible for inclusion. We excluded literature reviews and studies not published in English. For abstracts that passed this screening, we retrieved the full length articles. For inclusion in our study, the manuscript had to report either change in joint space width over a specified period of time or the proportion of the population that progressed in K–L grade over a specified period. Studies that exclusively assessed osteophyte progression, used categorical scales of OA severity other than K–L, and reported proportion of population that experienced JSN (rather than differences in means) were excluded.

DATA EXTRACTION

We extracted the following study and technical factors: study design [observational or randomized control trial (RCT)], year of publication, whether radiograph reader reliability tests were conducted or cited, sample size, length of follow-up, and radiographic view used. Year of publication was included to address potential secular trends in radiographic methods. Radiographic views included: standing antero-posterior (AP), metatarsal phalangeal (MTP), fixed-flexion postero-anterior (PA), semi-flexed AP, and Lyon Schuss. We also extracted descriptive characteristics of the study population, including proportion female, mean age, mean BMI and mean baseline joint space width (defined as the smallest interbone distance across the knee joint)[6]. We defined three cohort types based upon the definition of disease: incident OA (no disease at baseline and progression to any higher K–L grade), prevalent OA (disease at baseline and progression to any higher K–L grade at follow-up), and 'combination', which included subjects with both incident and prevalent OA (progression to any higher K–L grade, irrespective of grade at baseline). We also extracted data pertinent to the two main outcomes: (1) change in joint space width over the follow-up period and (2) proportion of the study population that progressed at least one K–L grade over the follow-up period. We refer to the latter as the risk of K–L progression.

ANALYSIS

Definition of outcome variables

Estimates of change in joint space width over the follow-up period (referred to as JSN throughout this report) were converted to annual rates. Similarly estimates for K–L progression were converted to annual risks of progression. For studies that reported estimates of progression for multiple cohorts, we included all estimates in our analyses. Thus, it was possible for a given manuscript to report more than one progression estimate (see Tables I and II). For studies that reported on change at various intervals in the same patients, only the estimate from the longest follow-up time was included. For RCTs, we extracted data from the placebo arm only. For studies that reported change in K–L scale in each (left, right) knee individually, we used estimates for the right knee only.

Analysis of JSN

For the JSN analysis, we grouped the five radiographic approaches observed in the literature into three categories: (1) full extension included the standing AP view, (2) semi-flexed with fluoroscopy included the semi-flexed AP and Lyon Schuss views, and (3) semi-flexed without fluoroscopy included the MTP and fixed-flexion PA views.

Analysis of progression in K–L grade

Since only one study assessing K–L progression used fluoroscopic methods, we collapsed the three radiographic approach categories to include only full extension and semi-flexed.

Three studies reported separate estimates of K–L progression when OA was defined as K–L ≥ 1 and K–L ≥ 2. To avoid double-counting these cohorts, we ran two separate K–L models. Both models included all K–L estimates from manuscripts that define OA either way, but not both. The first model included the estimates derived when OA was defined as K–L ≥ 2 for these three studies. The second model included the three estimates derived when OA was defined as K–L ≥ 1.

Statistical analysis

We performed meta-regression analyses examining the effects of radiographic approach, study design, year of study publication, length of follow-up, whether reader reliability was tested, and cohort characteristics such as mean age and proportion female, on each outcome: JSN or K–L progression. In addition, for the JSN model, we included mean baseline joint space width and mean BMI as predictors. For the K–L models, we included OA definition and cohort composition. We then examined various hypothesis-driven interactions in all models.

In both the JSN and K–L models, observations were weighted by the sample size of the cohort from which the observation was derived. All statistical analyses were performed at a 5% level of significance using SAS statistical software version 9.1 (SAS Institute, Cary, NC).

Results

The results of the search are depicted in Fig. 1. Of 239 manuscripts identified through our PubMed search, 34 met both the inclusion criteria and did not meet the exclusion criteria. These 34 studies comprise the study sample. An overview of the characteristics of each of the included studies is presented in Tables I and II.

JSN PROGRESSION

Crude analysis

Of the 27 estimates that assessed JSN, 85% included some measure of reader reliability. Sample sizes ranged from 11 to 312, with a mean of 103 ± 81 subjects across all study groups under consideration. All studies had a greater proportion of females than males. Length of follow-up ranged from 8 to 72 months with a mean of 26 ± 16 months. Fifteen estimates were derived from RCTs, and the remaining 12 were derived from observational studies. Eleven out of 27 estimates used full extension radiographic approach; eight used semi-flexed approach without

Table I
Study characteristics of the reviewed manuscripts: JSN

Author, year (Ref.)	Study population	Study design	Reliability	Sample size	Female (%)	Mean age (years)	Mean BMI	Baseline JSW (mm)	Follow-up (months)	Radiographic approach	Annual rate JSN (mm/year)
Bingham *et al.*, 2006[21]	Trial of oral risedronate at 42 centers in North America	RCT	Yes	310	57	60.2	30.4	2.95	24	SF + fluoro	0.04
	Trial of oral risedronate at 44 European centers	RCT	Yes	312	83	63.6	29.5	2.98	24	SF + fluoro	0.07
Brandt *et al.*, 2005[22]	Trial of doxycycline in obese women	RCT	Yes	180	100	55.0	36.7	3.60	30	SF + fluoro	0.18
Buckland-Wright *et al.*, 1995[23]	Trial of diclofenac sodium	RCT	Yes	34	73	65.5	NA	3.20	18	SF − fluoro	0.09
Cicuttini *et al.*, 2005[24]	Clinic-based and community-based cohort	Obs	Yes	28	63	62.8	28.6	7.87	23	Extension	0.24
Cline *et al.*, 2006[25]	DMOAD Roche trial	RCT	No	99	69	59.0	30.0	3.79	8	SF − fluoro	−0.10
	DMOAD Bayer trial	RCT	No	112	67	63.0	NA	3.27	10	SF − fluoro	0.00
	DMOAD Procter & Gamble trial	RCT	No	85	64	63.0	29.1	3.07	12	SF + fluoro	0.12
Conrozier *et al.*, 2005[26]	Clinic-based cohort	Obs	Yes	73	68	60.9	NA	4.10	12	SF − fluoro	0.19
Dieppe *et al.*, 1997[27], *	Clinic-based cohort, lateral compartment	Obs	Yes	145	67	62.6	26.9	NA	36	Extension	0.07
	Clinic-based cohort, medial compartment	Obs	Yes	145	67	62.6	26.9	NA	36	Extension	0.10
Gandy *et al.*, 2002[28]	Clinic-based cohort	Obs	Yes	11	60	63.4	28.4	4.71	37	Extension	0.07
Listrat *et al.*, 1997[29]	Trial of intra-articular injections of hyaluronan	RCT	No	17	79	64.0	26.6	3.50	12	Extension	0.70
Michel *et al.*, 2005[30]	Trial of chondroitin sulfate	RCT	Yes	150	52	63.1	28.1	2.45	24	SF − fluoro	0.04
Miyazaki *et al.*, 2002[31]	Clinic-based cohort	Obs	Yes	74	78	69.5	24.5	3.30	72	SF − fluoro	0.23
Pavelka *et al.*, 2004[32]	Clinic-based cohort	Obs	Yes	89	66	56.7	28.6	4.95	24	Extension	0.20
Pavelka *et al.*, 2000[10]	Trial of glycosaminoglycan polysulphuric acid complex	RCT	Yes	139	76	59.1	31.5	3.92	60	Extension	0.08
Pavelka *et al.*, 2002[33]	Trial of glucosamine sulfate	RCT	Yes	101	70	63.5	30.0	3.63	36	Extension	0.06
Pessis *et al.*, 2003[34]	Clinic-based cohort	Obs	No	20	65	63.0	30.0	3.80	12	Extension	−0.10
	Clinic-based cohort	Obs	No	20	65	63.0	30.0	2.80	12	SF + fluoro	0.0
Raynauld *et al.*, 2003[35]	Trial of long-term intra-articular steroid injections	RCT	No	34	61	63.3	31.9	3.93	24	SF + fluoro	0.04
Reginster *et al.*, 2001[36]	Clinic-based cohort	RCT	Yes	71	77	65.3	27.2	4.01	36	Extension	0.13
Sharma *et al.*, 2001[37]	Community-based cohort	Obs	Yes	230	75	64.0	30.3	NA	18	SF + fluoro	0.30
Spector *et al.*, 2005[38]	BRISK trial of risedronate	RCT	Yes	80	65	63.2	29.2	3.03	12	SF − fluoro	0.12
Sugiyama *et al.*, 2003[39]	Community-based cohort of rural village in Japan	Obs	Yes	110	100	50.2	24.7	3.40	48	SF + fluoro	0.13
Uebelhart *et al.*, 2004[40]	Trial of oral chondroitin sulfate	RCT	Yes	76	82	63.7	29.0	3.65	12	Extension	0.32
Vignon *et al.*, 2003[15]	NA	Obs	Yes	32	75	68.8	NA	2.92	24	SF − fluoro	0.12

Obs, observational cohort; SF + fluoro, semi-flexed with fluoroscopy; SF − fluoro, semi-flexed without fluoroscopy; NA, data not available from manuscript.

*Estimates of progression may include knees without OA. Analysis reported separate mean JSN estimates in medial and lateral compartments of each knee in a cohort of patients with OA in at least one knee. Right knee estimates are presented here.

Table II
Study characteristics of the reviewed manuscripts: K–L progression

Author, year (Ref.)	Study population	Disease definition		Study design	Reliability	Sample size	Female (%)	Mean age (years)	Follow-up (months)	Radiographic approach	Risk of K–L progression/year
		Cohort composition	K–L grade								
Bagge *et al.*, 1992[41]	Community-based cohort	Incident and prevalent	≥2	Obs	Yes	74	57	75.0	48	Semi-flexed	0.043
Bergink *et al.*, 2005[42]	Rotterdam study	Incident only	≥2	Obs	Yes	1115	59	66.3	79.2	Semi-flexed	0.010
	Rotterdam study	Prevalent only	≥2	Obs	Yes	288	59	66.3	79.2	Semi-flexed	0.014
Cooper *et al.*, 2000[19], *	Survey population	Incident only	≥2	Obs	Yes	242	72	75.8	61.2	Extension	0.040
	Survey population	Prevalent only	≥2	Obs	Yes	112	72	75.8	61.2	Extension	0.038
	Survey population	Incident only	≥1	Obs	Yes	178	72	75.8	61.2	Extension	0.035
	Survey population	Prevalent only	≥1	Obs	Yes	176	72	75.8	61.2	Extension	0.064
Felson *et al.*, 1995[43],*	Framingham study	Incident only	≥2	Obs	Yes	381	100	70.8	97.2	Extension	0.024
	Framingham study	Incident only	≥2	Obs	Yes	217	0	70.8	97.2	Extension	0.014
	Framingham study	Prevalent only	≥2	Obs	Yes	170	100	70.8	97.2	Extension	0.046
	Framingham study	Prevalent only	≥2	Obs	Yes	91	0	70.8	97.2	Extension	0.034
Lachance *et al.*, 2002[44],*	Michigan bone health study and study of women's health across the Nation	Incident only	≥1	Obs	Yes	489	100	NA	30	Extension	0.125
	Michigan bone health study and study of women's health across the Nation	Incident only	≥2	Obs	Yes	605	100	NA	30	Extension	0.052
LaValley *et al.*, 2001[45]	Framingham study	Incident and prevalent	≥1	Obs	No	843	64	71.1	102	Extension	0.029
Ledingham *et al.*, 1995[46]	Clinic-based study	Incident and prevalent	≥2	Obs	Yes	350	63	71.1	27.1	Extension	0.196
Mazzuca *et al.*, 2006[47]	Trial of doxycycline, obese women	Prevalent only	≥2	RCT	Yes	431	100	55.0	30	Semi-flexed	0.095
Pavelka *et al.*, 2000[10]	Trial of glycosaminoglycan polysulphuric acid complex	Prevalent only	≥1	RCT	Yes	139	76	59.1	60	Extension	0.042
Reijman *et al.*, 2005[48],†	Rotterdam study	Incident and prevalent	≥1	Obs	Yes	874	58	66.0	79.2	Extension	0.045
Spector *et al.*, 1992[49]	Clinic-based and those enrolled in drug study	Incident and prevalent	≥1	Obs	Yes	63	76	69.0	132	Extension	0.043
Spector *et al.*, 1994[50]	Chingford study	Prevalent only†	≥2	Obs	No	58	100	56.8	24	Extension	0.119
Spector *et al.*, 1997[51]	Chingford study	Prevalent only	≥2	Obs	Yes	70	100	56.0	48	Extension	0.136

Obs, observational cohort; NA, data not available from manuscript.

*Cohort characteristics (mean age, % female) based on entire patient sample (Cooper, $n = 354$; Felson, $n = 869$; Lachance, $n = 679$).

†Incident total knee replacement (TKR) included in definition of progression.

fluoroscopy; and eight used semi-flexed approach with fluoroscopy (see Fig. 2). JSN estimates ranged from −0.10 (indicating an increase in joint space width over time) to 0.70 mm/year. The mean annual JSN across all estimates was 0.13 ± 0.15 mm/year.

Multivariate findings

Overall, observational studies had a mean rate of JSN of 0.17 mm/year [95% confidence interval (CI), 0.11−0.22], compared with 0.08 mm/year (95% CI, 0.04−0.12) for RCTs (see Fig. 2), adjusting for radiographic approach, follow-up time, and gender. The effect of radiographic approach depended on study design (P for interaction = 0.02) (see Fig. 2). Adjusted mean rates of JSN were similar for full extension across both study designs (0.13 mm/year for observational studies and 0.18 mm/year for RCTs). Observational studies that used either semi-flexed approach reported larger narrowing estimates compared to RCTs that used the same approach. We did not find a statistically significant association between radiographic approach and JSN among observational studies. However, among RCTs, full extension was associated with greater narrowing compared to the semi-flexed without fluoroscopy approach. We found no statistically significant difference in narrowing between full extension and semi-flexed with fluoroscopy among RCTs, but the minimal overlap in CIs between the two groups is suggestive of a difference (see Fig. 2).

We found a suggestive negative linear relationship ($\beta = -0.0025$, $P = 0.06$) between JSN and longer follow-up time [see Fig. 4(A)]. Our data did not provide evidence of a linear relationship between JSN estimates and gender (β=0.0020, $P = 0.16$). We did not find an association between rates of JSN and mean age, mean BMI, reader reliability, and year of publication. Baseline joint space width was highly correlated with study design and radiographic approach, and thus was not included in the final model.

K−L PROGRESSION

Crude analysis

Of the 18 estimates of K−L progression derived from the literature, 89% included some measure of reader reliability. Sample sizes ranged from 58 to 1115 with a mean of 334 ± 314 subjects. All studies had a greater proportion of females than males. Length of follow-up varied from 24 to 132 months with a mean of 69 ± 31 months. Eleven out of 13 studies were observational studies, and the remaining two were RCTs. Ten out of 13 used full extension radiographic approach, while the remaining three used semi-flexed approach. In our 'K−L ≥ 2' model, five estimates were derived from OA definition K−L ≥ 1 and 13 from K−L ≥ 2. In our 'K−L ≥ 1' model, eight estimates were derived from OA definition K−L ≥ 1 and 10 from K−L ≥ 2. The annual estimates of progression by at least

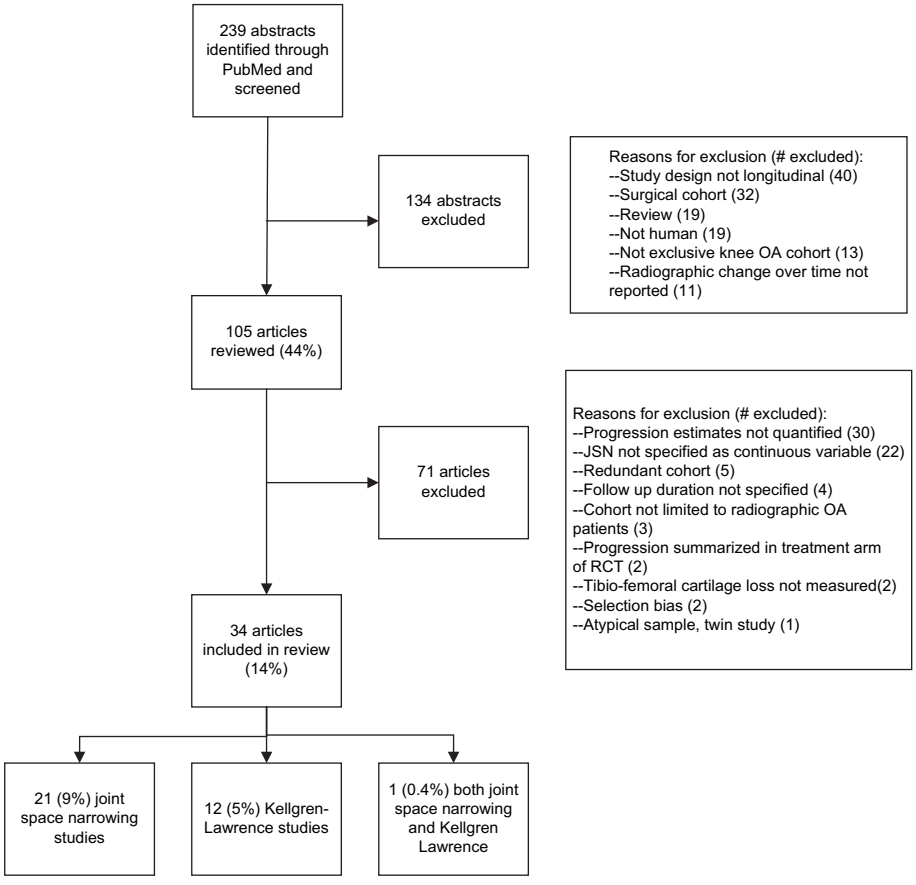

Fig. 1. Manuscript search and selection process.

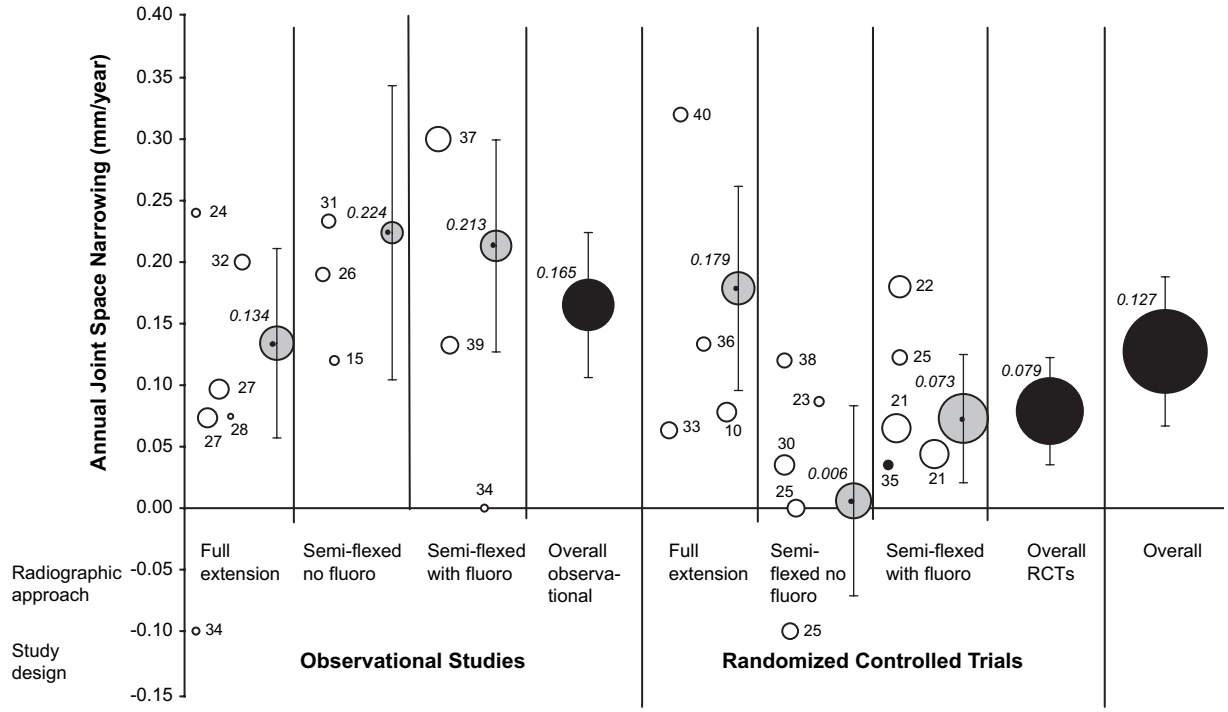

Fig. 2. Annual JSN stratified by study design and radiographic approach. Circles represent individual mean JSN estimates. Circle area is proportional to sample size of corresponding cohort. Means within study design and radiographic approach sub-categories are depicted in gray. Overall means within each study design category and the overall mean for all estimates are depicted in black. The means are displayed above corresponding circles, with error bars representing 95% CIs. Each study reference is denoted next the circle, representing the corresponding manuscript from which the progression estimate was derived. An estimate of 0.7 mm/year[29] (RCT, full extension) is not shown for scaling purposes.

one K–L grade ranged from 1.0 to 19.6%, with an overall mean risk of progression of $5.6 \pm 4.9\%$.

Multivariate findings

Main analysis: 'K–L $\geq$ 2' model. Risk of K–L progression was associated with a shorter follow-up time ($\beta = -0.0010$, $P < 0.01$) and with cohort composition ($P < 0.01$). We found a suggestive association between K–L progression and OA definition ($P = 0.09$). Studies with 'combination' cohorts (subjects with both incident and prevalent OA) had a greater risk of progression than those studies with incident or prevalent cohorts alone [8.0 vs 2.4% ($P < 0.01$) and 3.9% ($P = 0.05$), respectively] (see Fig. 3). Studies that defined OA as K–L $\geq$ 2 had a greater risk of progression than those studies that defined OA as K–L $\geq$ 1 (6.2 vs 3.3%). As seen in Fig. 4(B), a negative linear relationship exists between risk of K–L progression and follow-up time. We did not find an association between K–L progression and radiographic approach, gender, age, year of publication, study design, or reader reliability.

Sensitivity analysis: 'K–L $\geq$ 1' model. We repeated the K–L model with the estimates derived from OA defined as K–L $\geq$ 1 instead of from K–L $\geq$ 2 for the three studies that presented both, in order to assess the sensitivity of the model to OA definition. Multivariate findings were similar in both models, except for the effect of radiographic approach. In the K–L $\geq$ 1 model, studies using full extension had a greater adjusted risk of progression than those using semi-flexed approach (7.0 vs 3.6%, $P < 0.01$).

Discussion

The goal of this analytic review was to describe the variability in estimates of knee OA progression (JSN and K–L) from the published literature and to identify factors explaining this variability. We performed a thorough systematic search and analytic synthesis of the published peer-reviewed literature on radiographic progression of knee OA. Using these sources, we derived estimated annual rates of JSN and risks of K–L progression in populations with knee OA. We used meta-regression to study the association of these measures of OA structural progression with cohort characteristics and study features, in an attempt to explain the variability in estimates. A better understanding of the true rate of progression would assist clinicians in providing patients with an evidence-based trajectory of disease and timing of appropriate treatments. These estimates may also inform research on the development and testing of DMOADs.

We found a mean rate of JSN of 0.13 ± 0.15 mm/year across all estimates. This value falls within the range reported by other investigators. Pavelka *et al.* reported annual rates of progression of JSN of 0.06–0.60 mm/year[10]. Our finding is also consistent with the range reported by Vignon *et al.* of 0.10–0.15 mm/year in hip and knee joints[6]. Secondly, we found a mean annual risk of progression in K–L grade of $5.6 \pm 4.9\%$. To the best of our

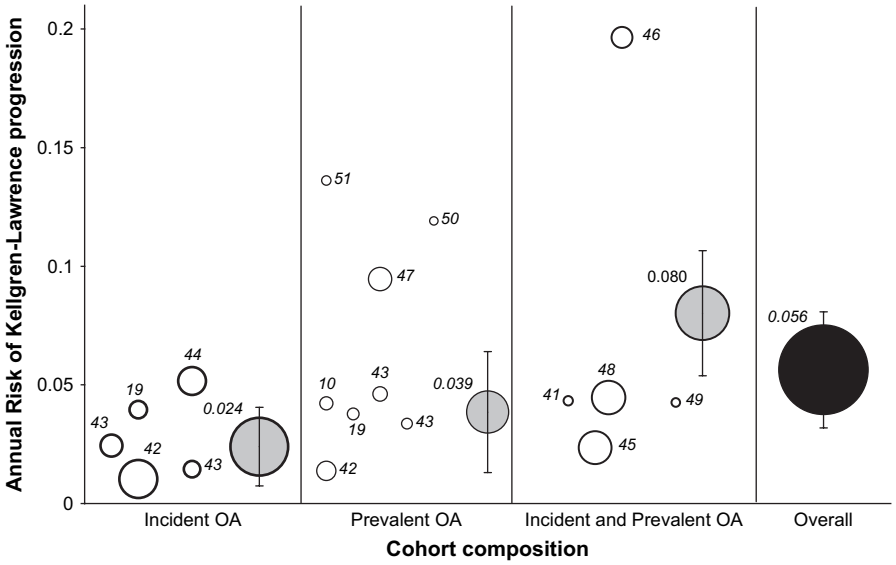

Fig. 3. Annual risk of K–L progression stratified by cohort composition. Circles represent individual estimates of the proportion of the cohort that progressed by at least one K–L grade per year of follow-up time. Circle area is proportional to sample size of corresponding cohort. Means within each cohort composition category are depicted in gray. Overall mean for all reviewed K–L studies is depicted in black. The means are displayed above corresponding circles, with error bars representing 95% CIs. Each study reference is denoted next the circle, representing the corresponding manuscript from which the progression estimate was derived.

knowledge there are no published reports summarizing OA progression based on K–L grade. Both metrics exhibited variability, with standard deviations similar to the means.

This is the first literature review to our knowledge that comprehensively reports OA progression estimates and attempts to quantitatively explain the variability inherent in these estimates, adjusting for important covariates. To rigorously investigate these questions, we also used weighted regression techniques, which helped to eliminate the effect of sample size on the parameter estimates.

We demonstrated that estimates of JSN exhibit variability, partly explained by differences in radiographic approach and study design (see Fig. 2). We found that among observational studies, those that used full extension approach, while not statistically significant, tended to report lower estimates of narrowing than those that used either semi-flexed approach. This is consistent with findings by Wolfe *et al.*, who reported that, in a clinic-based observational cohort, greater narrowing was seen in Lyon Schuss semi-flexed view (uses fluoroscopy) and MTP semi-flexed view (no fluoroscopy) when both were compared to standing AP view (full extension). No difference was reported between the Lyon Schuss view and the MTP view, further supporting our finding that the use of fluoroscopy in the semi-flexed approach has little impact on the JSN estimates (see Fig. 2)[13]. Recently, a shift toward non-fluoroscopic methods has occurred because they are less costly and easier to use, with little tradeoff in imaging quality and reproducibility[14]. Overall, full extension exhibited greater variability compared with both semi-flexed methods. Variability in serial radiographs in full extension may result from differences in knee positioning or changes in pain status at repeated X-ray visits, as patients with OA may be unable to adopt the fully extended position due to a joint pain flare[6]. Semi-flexed views employ various methods to standardize knee positioning and foot rotation to minimize variability. Such methods include MTP and patella alignment with film cassette (MTP semi-flexed)[13], X-ray beam angulation in line with medial tibial plateau (Lyon Schuss semi-flexed view)[15], and fluoroscopy.

The lower mean narrowing observed among subjects participating in RCTs utilizing either semi-flexed approach may suggest systematic differences in selection criteria for RCTs as compared to observational studies. Trials tend to set more stringent inclusion and exclusion criteria, resulting in a more homogeneous population. Moreover, the populations that participate in RCTs and observational studies may differ according to other important and unmeasured confounders, potentially resulting in the observed differences. RCTs may also be better funded to obtain radiographs of consistent method, quality, and timing. However, while RCTs are the best approach to testing efficacy questions, their samples are selected and typically are not as generalizable to clinical populations as observational studies.

The variability in progression along the K–L scale was explained in part by differences in follow-up time, OA definition, and cohort composition [see Figs. 3 and 4(B)]. We found that a higher risk of K–L progression was associated with full extension in the K–L $\geq$ 1 model. The full extension view of the knee may be optimal for visualizing osteophytes, and thus may explain why a higher risk of K–L progression was seen in those studies that used full extension view compared with semi-flexed view. This may also explain why the majority of studies that reported K–L progression employed full extension view. This is consistent with findings by Wolfe *et al.*, who reported that standing AP (fully extended) radiographs accumulated a greater mean osteophyte score [OARSI (Osteoarthritis Research Society International) atlas] compared to Lyon Schuss semi-flexed radiographs[13]. The differential ability of the two radiographic approaches to show osteophytes may also explain why radiographic approach did not matter in the analysis using K–L $\geq$ 2 as the OA definition, but was significantly associated with risk of progression when OA was defined as

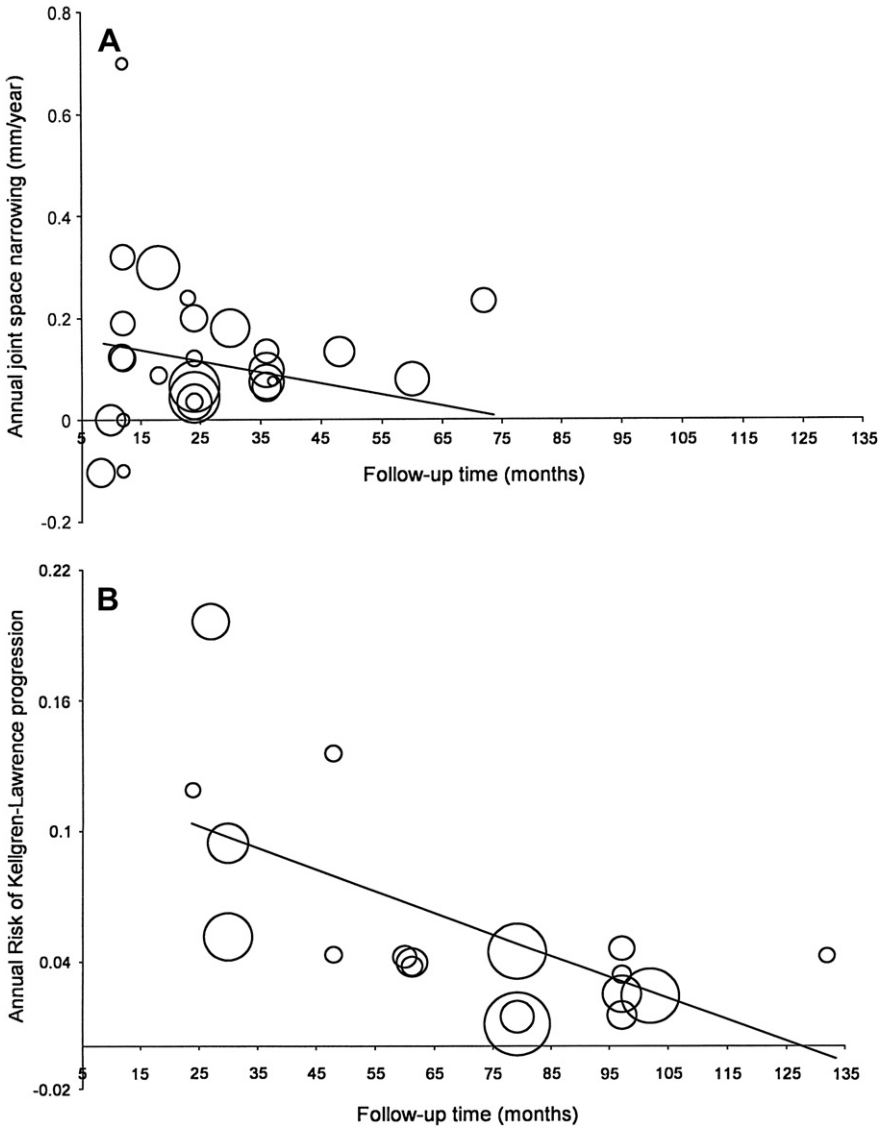

Fig. 4. Association of OA progression [JSN (A) and K–L (B)] and study duration. Circles represent individual estimates of the proportion of the cohort that progressed by at least one K–L grade per year of follow-up time. Circle area is proportional to sample size of corresponding cohort. Regression line for follow-up time is weighted for sample size and adjusted for radiographic approach (A and B), OA definition (B), and cohort composition (B).

K–L $\geq$ 1. Full extension may show more ''possible osteophytes'' (i.e., K–L = 1) than semi-flexed. When OA is defined as K–L $\geq$ 2, it is possible that each radiographic approach shows ''definite osteophytes'' equally well. However, it should be noted that sensitivity of the model to radiographic approach may simply be due to the small number of studies and estimates, resulting in a difference in only three estimates affecting the significance of the finding.

The difference in follow-up time seen in JSN studies and K–L studies also warrants discussion. As seen in Fig. 4(A) and (B), a negative linear relationship exists between both JSN and risk of K–L progression and follow-up time. It is important to note that the mean follow-up time for JSN studies was 26 months compared to 63 months for K–L studies. The shorter duration of JSN studies precludes comparisons across longer follow-up durations. The risk of K–L progression decreases as follow-up time increases, demonstrating that progression of OA as measured by the K–L scale may not be constant over time. This may reflect the biology of OA progression, suggesting it may plateau. On the other hand, this association may simply indicate that the K–L scale is ordinal but not interval. K–L grades 1–2 track the growth of osteophytes, while K–L grades 3–4 track JSN. Since the two ends of the scale reflect different pathological processes that involve different tissues, the amount of disease progression from one grade to the next should not be considered equal throughout the scale[12]. There is also a ceiling effect at K–L grade 4, since progression beyond >50% narrowing cannot be captured. It is possible that longer studies tend to accumulate more patients with K–L grade 4 who cannot progress any further along the scale, resulting in slower rates of progression.

Our review had several limitations. First, we identified several limitations in this literature which may have affected

our results. Across eligible studies, documented risk factors for progressive knee OA were not universally reported. Risk factors for knee OA progression include BMI, varus–valgus alignment, dynamic load, concurrent OA in other joints, synovitis, ligamentous laxity, and bone marrow edema lesions[16]. BMI, in particular, has been confirmed as a risk factor for incident OA, but multiple studies have found that BMI is only a weak predictor of JSN compared with radiographic evidence such as initial joint space width or narrowing[17,18]. We did not find an association between mean BMI and JSN. However, four studies did not report mean BMI, limiting our capacity to see an effect. A majority of the reviewed K–L studies (8/13) did not report mean BMI of their cohorts; thus we were unable to include this in the K–L models. However, the literature suggests the effect of BMI on our progression estimates would likely be modest[19].

We focused our analyses on radiographic – not MRI – progression of OA. We acknowledge that MRI is a powerful modality for imaging the arthritic knee. However, the interpretation of longitudinal changes in joint structures seen on MRI is undergoing intensive discussion[20] and assessment of plain radiographs remains the most well accepted approach to structural progression at present.

In addition, approximately 60% of the JSN manuscripts limited their patient samples to those with K–L grades of less than four or joint space width $>$ 2 mm at baseline, while none of the K–L manuscripts noted any exclusion of those with advanced disease. Thus, narrowing estimates derived from these studies may not be representative of the entire OA population.

A better understanding of the true rate of progression would assist clinicians in providing patients with an evidence-based trajectory of disease and timing of appropriate treatments. These estimates may also inform research on the development and testing of DMOADs. In particular, these data should help investigators estimate sample sizes when designing DMOAD trials. Our data also support the need for standardized radiographic protocols to assess the progression of OA. The optimal protocol is one that is sensitive to change, reproducible, accurate, and constant across study settings and study populations. As there may be tradeoffs in establishing a standard radiographic approach, this decision should be undertaken carefully with involvement of a full complement of stakeholders.

Conflict of interest

The authors have no conflict of interest.

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